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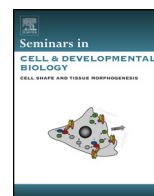




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Review

Oocyte development, meiosis and aneuploidy

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ABSTRACT

Meiosis is one of the defining events in gametogenesis. Male and female germ cells both undergo one round of meiotic cell division during their development in order to reduce the ploidy of the gametes, and thereby maintain the ploidy of the species after fertilisation. However, there are some aspects of meiosis in the female germline, such as the prolonged arrest in dictyate, that appear to predispose oocytes to missegregate their chromosomes and transmit aneuploidies to the next generation. These maternally-derived aneuploidies are particularly problematic in humans where they are major contributors to miscarriage, age-related infertility, and the high incidence of Down's syndrome in human conceptions. This review will discuss how events that occur in foetal oocyte development and during the oocytes' prolonged dictyate arrest can influence meiotic chromosome segregation and the incidence of aneuploidy in adult oocytes.

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1. Introduction

Abnormalities in chromosome number, or aneuploidies, have been associated with human disease for over fifty years, and are the most common known genetic cause of developmental and intellectual disabilities in human births [1–5]. Embryos ought to inherit one copy of each of the twenty two autosomes and one sex chromosome from each parent, and aneuploidy can involve inheriting too many or too few of any of these chromosomes. Most aneuploid embryos that inherit only one copy of an autosome (autosomal monosomy) develop severe abnormalities and die before pregnancy is clinically recognised. Inheriting an extra copy of an autosome (autosomal trisomy) is also associated with severe developmental abnormalities and accounts for approximately a third of all miscarriages. Some autosomal trisomies, and some sex chromosome aneuploidies, are compatible with birth in humans. Chromosome 21 trisomy, the cause of Down's syndrome, is by far the most frequent aneuploidy affecting live births [4–6].

Aneuploid embryos arise primarily due to inheritance of maternally-derived aneuploidies: around 10–30% of fertilised oocytes are aneuploid, compared to only 1–2% of spermatozoa [4–6]. This strong maternal bias applies primarily to autosomal aneuploidies, but sex chromosome aneuploidies are exceptions to this: the extra sex chromosome that causes Klinefelter's syndrome (XXY sex chromosome trisomy) is paternally derived in 46% of cases [4]. Down's syndrome does follow the general maternal bias for aneuploidy with around 88% of chromosome 21 trisomies arising maternally, 8% paternally, and the remainder thought to arise due to mitotic errors during early embryonic development [4]. The frequency of aneuploid conceptions is strongly associated with maternal age, and aneuploidy rates increase exponentially during the decade prior to menopause. Maternal age affects autosomes more strongly than sex chromosomes, and some autosomes more strongly than others [4–6]. The high prevalence and severe consequences of oocyte aneuploidy make maternally-derived aneuploidy a subject of significant importance. This review will discuss recent developments in the field that inform on the causes of oocyte aneuploidy in mammals.

2. Overview of oocyte development

Mammalian oogenesis begins with the differentiation of oocytes from sexually dimorphic primordial germ cells in the foetal ovaries. In female mice, germ cells become committed to differentiate down a female pathway into oocytes between E12.5 and E13.5, which is typically accompanied by a transition from mitosis to meiosis [7,8]. Meiosis involves one round of DNA replication followed by two meiotic divisions, MI and MII [6,9–12]. Oocytes initiating meiosis contain two homologous copies of each chromosome, one inherited from each parent, each of which replicates to form two sister chromatids during meiotic S phase, and are held together by sister chromatid cohesion. After meiotic S phase, oocytes enter the leptotene stage of MI, and initiate meiotic recombination by generating DNA double strand breaks (DSBs) that recruit repair proteins to form recombination foci [13]. This stimulates the pairing and synapsis of homologous chromosomes in zygotene as DSBs search for a homologous template to repair from. Synapsis and assembly of the synaptonemal complex, a protein scaffold that holds synapsed chromosomes together, is complete by pachytene (Fig. 1). During zygotene and pachytene, the recombination foci mature, and recruit a series of factors that promote the resolution of recombination intermediates into either crossover or non-crossover exchanges [13]. Non-crossover exchanges only acquire short patches of homolog sequence used as a template to repair the DNA damage, whereas crossovers exchange the chromatid

arms between homologous chromatids distal to the crossover site (Fig. 1). These crossover events have two purposes: they increase genetic diversity in the population; and, once the synaptonemal complex disassembles in diplotene, they provide the physical connection that keeps homologous chromosomes together [11,12]. Around the time of birth, developing oocytes arrest at dictyate with chiasmata, the physical manifestation of crossovers, holding homologous chromosomes together as a single bivalent unit (Fig. 1). During this lengthy dictyate arrest, which can last for months in mice or decades in humans, the chiasmata are maintained by cohesion between sister chromatids, particularly cohesion on the chromosome arms distal to the chiasmata [6,9].

Hormonal stimulation during the adult oestrus cycle subsequently induces groups of dictyate oocytes to grow, mature, and eventually resume meiotic prophase and progress into metaphase I. The bivalent chromosomes are held together by chiasmata and arm cohesion as they align on the meiotic spindle in metaphase I (Fig. 1) [6,11,12,14]. These physical links between homologous chromosomes, in combination with mono-orientation of sister centromeres, allow tension to be generated when centromeres from each homolog attach to opposite spindle poles. At least one chiasma is therefore required on each homologous chromosome pair to ensure balanced chromosome segregation in MI. As oocytes go through the metaphase I to anaphase I transition, sister chromatid cohesion on chromosome arms is released allowing chiasmata to resolve, and homologous chromosomes to segregate to opposite spindle poles. Sister chromatid cohesion at the centromeres is retained at this point and holds the two sister chromatids together (Fig. 1) [6,11,12,14]. As the oocytes progress into the MII, each pair of sister chromatids aligns on the metaphase II spindle with sister centromeres bi-oriented to opposite spindle poles. The oocyte then arrests at metaphase II and typically completes meiosis in response to fertilisation, removing centromeric cohesion to allow sister chromatids to separate and segregate to opposite spindle poles (Fig. 1) [6,11,12,14]. Both the meiotic divisions in oocytes are asymmetric, and extrude one set of chromosomes into small polar bodies that will degenerate during pre-implantation development, and retain one haploid set of chromosomes in the larger developmentally competent oocyte [6]. Generating and maintaining cohesion between sister chromatids and chiasmata between homologs during oocyte development are therefore key for preventing transmission of aneuploidies to the next generation.

3. Crossing over in foetal oocytes

3.1. Introduction to meiotic recombination

Meiotic recombination takes place during foetal stages of oocyte development, and is a key process in enabling the balanced metaphase I segregation of homologous chromosomes in adults. Recombination is initiated by the activity of the highly conserved endonuclease SPO11, which generates hundreds of DSBs across the genome during the start of meiotic prophase [13]. These DSBs subsequently recruit repair proteins which initiate a search for their homologous chromosome partner, promoting the pairing and synapsis of homologous chromosomes in mice [13]. The repair of meiotic DSBs to crossovers typically requires the heterodimeric complex of the mismatch repair proteins MLH1 and MLH3 [13]. These proteins can be visualised immunocytologically as foci localised to chromosomal axes in zygotene and pachytene foetal oocytes, and are interpreted as a reliable proxy for crossover frequency and positioning in both mouse and human germ cells [15,16]. The transient localisation of MLH1 in mouse and human oocytes, as well as the formation of ~10% of crossovers by an alternative pathway [15–17], make MLH1 foci counts conservative

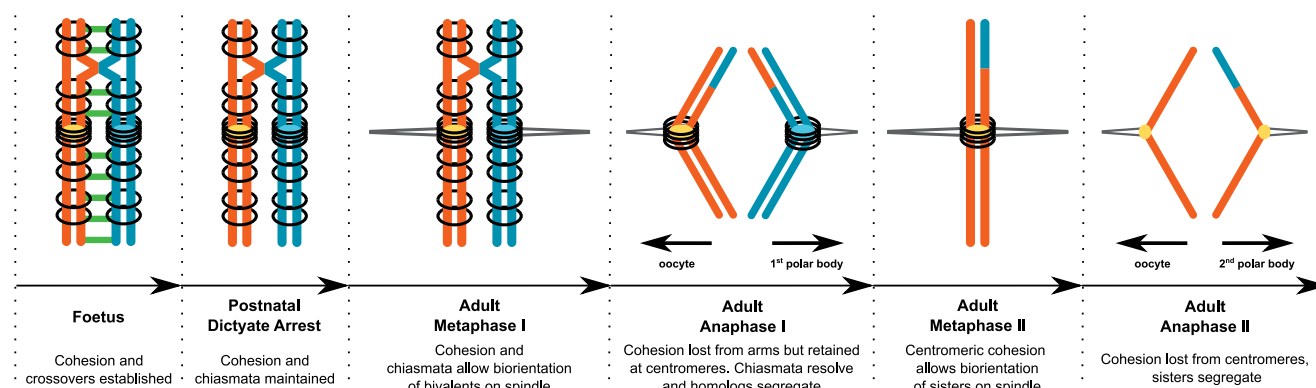


Fig. 1. Meiotic oocyte progression from foetus to adult. Schematic diagram showing how events that occur during foetal development influence meiosis I chromosome segregation in adult oocytes. Two homologous chromosomes (blue, orange), each comprising two sister chromatids, centromeres (light blue, light orange), sister chromatid cohesion (black circles), synaptonemal complex (green lines) and meiotic spindles (grey lines) are indicated. Sister chromatid cohesion and crossover exchanges/chiasmata established during foetal development provide a physical link between homologous chromosomes that persists after the synaptonemal complex disassembles and throughout diploty. Chiasmata and sister chromatid cohesion facilitate bi-orientation of bivalent chromosomes on the meiotic spindle during metaphase I in adult oocytes. Removal of arm cohesion and resolution of chiasmata allows homologous chromosomes to segregate to opposite spindle poles in anaphase I, whilst centromeric cohesion continues to hold sister chromatids together at this stage. Removal of centromeric cohesion allows separation of sister chromatids in anaphase II. Both meiotic divisions are asymmetric and segregate one set of chromosomes into the oocyte, and the other into small polar bodies that degenerate during pre-implantation development.

estimates of crossover formation. As the synaptonemal complex dissociates, crossovers can be visualised as the chiasmata, though this is also a proxy for crossover formation as chiasmata are susceptible to migration or loss [6,9]. Whilst these cytological techniques are only applicable to analysis of recombination in MI germ cells, genotyping allows the crossover genetic exchanges occurring in foetal oocytes to be detected in subsequent stages of oocyte development and in adult offspring [5,18]. Genotyping relies on there being sufficient polymorphisms between the homologous chromosomes to identify the segments of chromosomes inherited together. Genotyping characteristic pericentromeric markers also enables identification of parental origin of surplus/absent chromosomes in aneuploidies and whether they are sister or homologous chromosomes [19,20].

3.2. Chromosomes without a crossover

As mammalian oocytes progress through the foetal stages of meiotic prophase it is essential that at least one crossover is formed by recombination between each pair of homologous chromosomes to ensure their balanced segregation during MI (Fig. 1, Fig. 2A). Genetic studies of Down's syndrome patients have estimated that ~30% of all maternally-derived cases with homologous chromosome segregation error have failed to form crossovers on the affected chromosome, indicating that this fault is often responsible for the resulting aneuploidy (Fig. 2B) [21]. Analysis of foetal oocytes has demonstrated that chromosomes 21 and 22 are the most common to lack MLH1-marked crossovers and do not have detectable MLH1 foci ~5% of the time [16]. The production line hypothesis proposed the formation of low numbers of crossovers in oocytes generated later in gestation, which would subsequently be ovulated later in adult life and predispose older mothers to aneuploidy [22]. However, MLH1 foci counts in oocytes of different gestational age indicates that no such drop in crossover formation exists [23]. Thus, the failure to form a crossover during foetal oocyte development contributes to oocyte aneuploidy independent of maternal age [21]. Low genome-wide recombination rates, rather than a specific reduction in crossovers on chromosome 21, are associated with Down's syndrome caused by a maternal failure to form a crossover on chromosome 21 [24]. Curiously, low genome-wide recombination rates are also seen in the siblings of these Down's syndrome patients, independent of maternal age, indicating that maternal factors influence the rate of crossover formation and the frequency at

which chromosomes without a crossover arise during oogenesis [25].

3.3. Crossover frequency control

Crossover frequency as measured either by MLH1 foci counts or by genotyping is reported to vary ~10-fold in human oocytes both across the populations studied and within individuals [23,26,27]. The variation reported is much greater than that of human males and also mice of both sexes, indicating that the regulation of crossover frequency may be less strictly controlled in human females, potentially contributing to the high rate of maternally derived aneuploidies. Genome wide association studies to identify variants that influence maternal crossover frequency have led to the identification of a number of variants associated with this, including several in *RNF212* [28,29]. *RNF212* is implicated in the control of recombination taking place in foetal oocytes, and has been demonstrated in mice to localise to meiotic recombination intermediates and promote their resolution by crossover formation [30]. Variants in this gene may be an example of a maternal factor accounting for low crossover rates in oocytes resulting in offspring with Down's syndrome or their healthy siblings.

Following the formation of several hundred DSBs in the foetal oocyte, some DSBs repair as non-crossovers or by inter-sister recombination and only ~10% of the original DSBs repair to form crossovers. Although many proteins are involved in DSB formation and homologous chromosome synapsis upstream of crossover formation, mutations or polymorphisms in these proteins typically cause defects in chromosome synapsis and infertility in mice [13] and these proteins may have limited effects on crossover frequency in human populations. A smaller group of proteins are implicated in promoting the repair of DSBs to form crossovers in mice, and these are good candidates for regulating crossover frequency in humans. The heterodimer of mismatch repair protein homologs MSH4 and MSH5 is essential for stabilising recombination intermediates and the formation of crossovers in mice [13]. MSH4 also physically associates with TEX11 during meiosis, a protein of unknown biochemical function that promotes crossover formation in mouse oocytes [31]. The stability of MSH4 and TEX11 at recombination intermediates in mice is controlled by the antagonistic relationship of the SUMO E3 ligase RNF212 [30] and the E3 ubiquitin ligase HEI10 [32]. The AAA+ ATPase TRIP13 is also involved in promoting crossover formation in mouse oocytes [33], though it is not

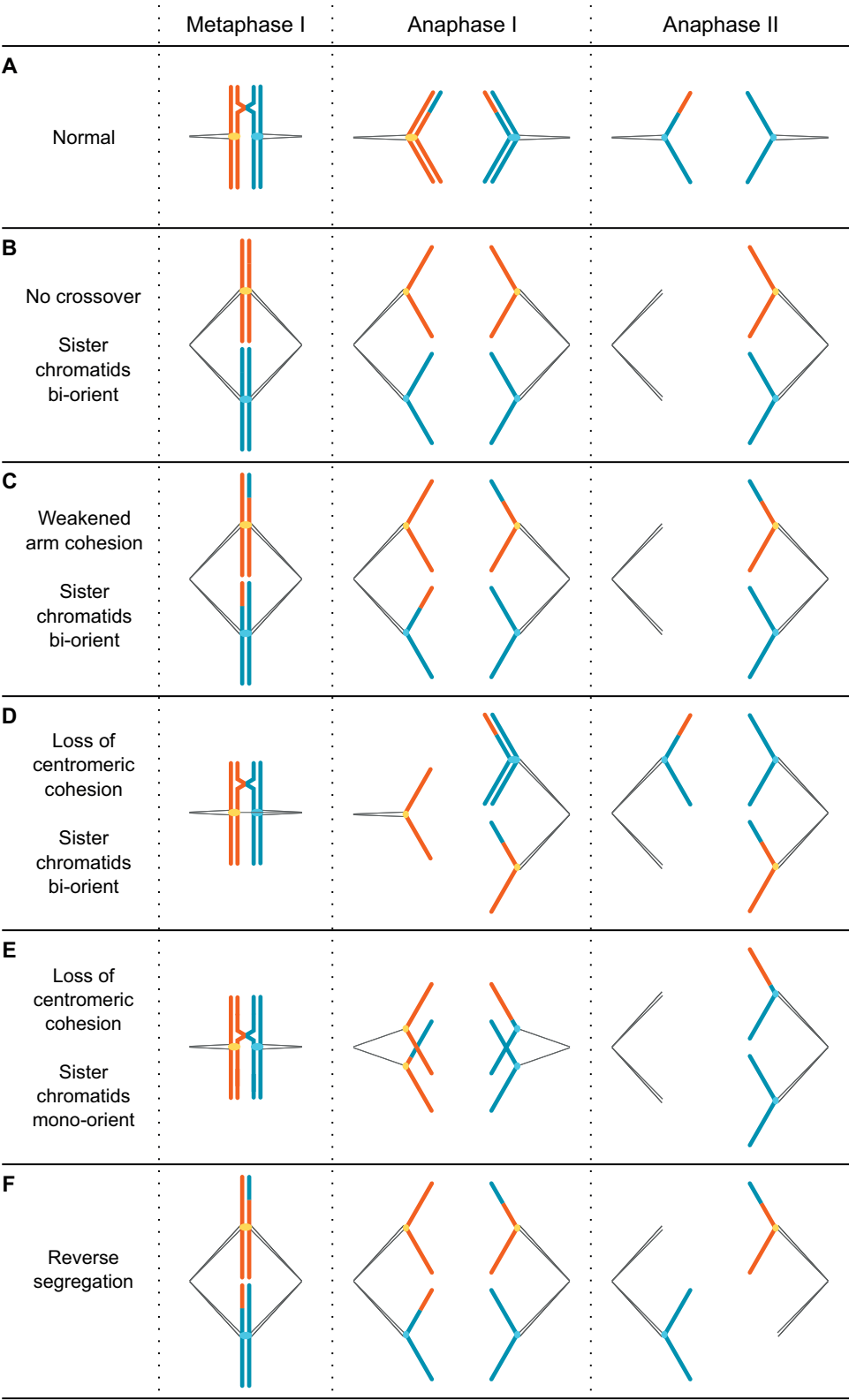


Fig. 2. Potential mechanisms contributing to chromosome missegregation in mammalian oocytes. Schematic diagram showing normal meiotic chromosome segregation (A), and some abnormal meiotic chromosome segregation patterns that can generate oocyte aneuploidy (B–E). Two homologous chromosomes (blue, orange), each comprising two sister chromatids, centromeres (light blue, light orange), and meiotic spindles (grey lines) are indicated. Failure to generate crossovers during foetal development (B), or loss of chiasmata caused by age-dependent weakening of arm cohesion (C), can cause missegregation due to bi-orientation of univalents on the MI spindle, and premature sister chromatid separation during MI. Age-dependent weakening of centromeric cohesion (D), possibly exacerbated by peri-centromeric crossovers (E), can cause missegregation due to bi-orientation of sister chromatids on the meiosis I spindle (D) and/or premature separation of sister chromatids during meiosis I (E). Weakening of centromeric cohesion could potentially affect one (D) or both (E) homologous chromosomes in the same division. A number of additional meiotic chromosome segregation errors are possible which, for clarity, are not depicted here. Any of the abnormal segregation patterns that involve bi-orientation of sister centromeres and premature segregation of sister chromatids at meiosis I can still generate normal haploid oocytes if homologous chromatids partition to different cells in meiosis II (F).

yet clear how it relates to other components of the recombination machinery. *MSH4*, *MSH5*, *TEX11*, *HEI10*, *RNF212*, and *TRIP13* are therefore good candidates for regulators of maternal recombination in humans and potential risk factors for increased incidence of oocyte aneuploidy.

3.4. Susceptible exchanges

Maternally-derived Down's syndrome usually involves copies of chromosome 21 that have undergone a single detectable crossover exchange [21]. However, the position of these single crossovers along the chromosome can predispose it to missegregation. Single crossovers in regions close to the telomere rarely occur in human oocytes contributing to healthy conceptions, but are enriched in maternally-derived Down's syndrome trisomies caused by homolog missegregation [21]. Telomeric chiasmata are conceivably most sensitive to being lost from chromosome arms as there is less distal arm cohesion maintaining them. The incidence of Down's syndrome involving copies of chromosome 21 with telomeric crossovers is largely independent of maternal age, suggesting that some weakening of arm cohesion and loss of chiasmata occurs even in oocytes from young mothers. Similarly, single telomeric crossovers on chromosome 16 are thought to cause the high incidence of chromosome 16 univalents in oocytes of young mothers, and the high rates of trisomy associated with this chromosome [34,35]. However, as maternal age increases, copies of chromosome 21 that have crossovers positioned further from telomeres become more susceptible to missegregation, and missegregation is not restricted to those copies of chromosome 21 that have telomeric exchanges [21,36]. This is likely due to failed chiasmata maintenance caused by age-dependent weakening of sister chromatid cohesion (Fig. 2C, Section 4.4).

Remarkably, positioning of crossovers proximal to the centromere has been shown to leave chromosomes susceptible to sister chromatid missegregation in cases of maternally-derived Down's syndrome [19,20]. Peri-centromeric exchanges are risk factors for trisomy 21 even when this chromosome has two crossovers rather than one [37]. Contrary to telomeric exchanges, peri-centromeric crossovers are rarely observed in cases originating from younger mothers, but observed much more frequently with maternal age [21]. Therefore such cases fit with the proposed two-hit model of chromosome missegregation [20]. The first hit is formation of a susceptible crossover pattern during foetal development, and the second hit is the age-dependent increase in risk of that susceptible chromosome missegregating. It is possible that peri-centromeric crossovers disrupt centromeric cohesion between sister chromatids in MI, further compromising age-dependent weakening of cohesion (Fig. 2E), although there are other mechanistic interpretations of this genetic association [6,21]. In summary, particular recombination patterns established at foetal stages of oocyte development can predispose both homologous chromosomes and sister chromatids to missegregation during the meiotic divisions in adult oocytes.

3.5. Factors regulating crossover position

Crossover positioning is subject to regulation at multiple stages of meiotic recombination. For a crossover to form at a locus a DSB must first be generated to participate in recombination. DSB formation is enriched at certain hotspots throughout the genome [13], which are determined at least in part by the zinc-finger histone methyltransferase PRDM9 [13]. Research in human spermatocytes has demonstrated that crossover frequency in a particular position largely correlates with DSB frequency at that site [38], although analysis of specific hotspots in mice suggests that there can be significant regional and sex-specific differences in the proportion

of DSBs that mature into crossovers at some sites [39]. Crossover formation at certain locations makes chromosomes susceptible to missegregation, therefore such defects could be traced back to positioning of DSBs at vulnerable loci.

The distribution of crossovers over the genome tends to follow a pattern with three potentially related features: (i) at least one crossover is typically formed between each pair of homologous chromosomes [15], (ii) crossover frequency is buffered from fluctuation in DSB frequency by a process of crossover homeostasis [40], and (iii) multiple crossovers are distributed across chromosomes by crossover interference inhibiting their formation in close proximity [12,15]. The mechanism(s) influencing this distribution are not known, though research in mice indicates that chromatin loop organisation influences crossover promotion [41], and work in yeast has led to a model where crossover formation is regulated by physical chromosomal stress in a pathway involving topoisomerase II [42]. The strength of crossover interference correlates with physical distance along the synaptonemal complex, thus this structure is thought to be involved in interference transmission [43]. Indeed, higher crossover frequency in human oocytes compared to spermatocytes correlates with differences in synaptonemal complex length [43,44]. Defects in mechanisms influencing this control of crossover distribution could generate chromosomes without a crossover that ultimately missegregate resulting in aneuploidy.

3.6. Chromosome missegregation in human oocytes

Genotyping Down's syndrome patients has demonstrated that around three-quarters of maternally-derived cases are caused by missegregation of homologous chromosomes, and a quarter by missegregation of sister chromatids [4,19]. This is consistent with a wealth of cytological data indicating that the most prevalent chromosome missegregation events in human oocytes from older women involve premature separation and segregation of sister chromatids during MI (Fig. 2C–E) [6]. A recent genetic study combining analysis of all three products of a complete female meiotic division: the first and second polar body, and the oocyte, has provided further insight into the mechanisms of chromosome missegregation in human oocytes [27]. This study revealed that even in cases where recombination took place between homologs, a failure to form multiple crossovers involving all four chromatids in exchanges predisposes to premature separation of an individual sister chromatid during MI [27]. However, the most common segregation error involved premature separation and segregation of sister chromatids from both homologs in MI (Fig. 2C), a conclusion similar to that reached from imaging and analysis of ageing mouse oocytes [45,46]. This MI segregation error occurs much more frequently than expected if each homolog in a bivalent lost cohesion independently (Fig. 2D), suggesting an alternative mechanism is involved [27]. Live imaging of young and old mouse oocytes has demonstrated that bivalents separate into univalents during metaphase I more frequently in older oocytes, then bi-orient on the MI spindle [47]. This results in premature separation and segregation of sister chromatids during MI, which could partition independently during MII to generate either an aneuploid oocyte (Fig. 2C), or a haploid oocyte with normal chromosome complement (Fig. 2F). A similar mechanism may be responsible for the common MI segregation errors reported in human oocytes [27]. The production of a normal haploid oocyte following premature segregation of sister chromatids in MI and correction by segregation of homologs in MII (Fig. 2F), a phenomenon described as "reverse segregation", was indeed found to frequently occur in humans [27]. Failure to form crossovers between homologs during foetal development presumably results in a similar pattern of chromosome missegregation (Fig. 2B) and potentially also reverse segregation. Generating and maintaining at least one chiasmata per homologous

chromosome pair during foetal oocyte development, through the prolonged dictyate arrest and up to metaphase I therefore appears to be crucial for faithful meiotic chromosome segregation in the adult oocyte.

4. The role of cohesins in foetal and postnatal oocyte development

4.1. Cohesins in meiosis

The sister chromatid cohesion that will mediate meiotic chromosome segregation in adult oocytes is established during foetal development. Sister chromatid cohesion is generated by the cohesin complex which forms a tripartite ring like structure that holds sister chromatids together [48]. The cohesin complex comprises four subunits: a core V-shaped heterodimer of two SMC (Structural Maintenance of Chromosomes) subunits; a kleisin subunit which closes and stabilises the ring-like structure; and one SA (Stromalin Antigen) subunit that associates with the kleisin. In mitotic cells the two SMC subunits are SMC1 α and SMC3, the kleisin subunit is RAD21, and the SA subunit is either SA1 or SA2. Meiotic cells express additional SMC and SA subunits named SMC1 β and STAG3 respectively, and two additional kleisin subunits, REC8 and RAD21L [9,49].

The presence of multiple flavours of cohesin subunits in meiotic cells means that many different hypothetical cohesin complexes can be generated containing different combinations of alternative SMC1, kleisin and SA subunits. Immunoprecipitation of cohesin subunits from testes extracts reveal that SMC1 α and SMC1 β do exist in several different complexes with other cohesin subunits *in vivo* [50]. However, not all hypothetical cohesin complexes are detectable in meiotic cells, for example the meiotic SA subunit STAG3 is present in cohesin complexes with REC8 or RAD21L meiotic kleisins, but not with the mitotic kleisin RAD21 in mouse testes [51,52]. Interestingly, different flavours of the same cohesin subunit can localise to distinct regions of meiotic chromosomes in mouse oocytes and spermatocytes [51–54] suggesting that different cohesin complexes could have distinct functions in mammalian meiosis.

Cohesins can promote intra-molecular interactions between different regions of DNA on the same chromosome in addition to inter-molecular interactions between DNA on sister chromosomes [48]. The former may be important for generating loops of chromatin that are thought to underlie the structure of meiotic chromosomes [55], and some of the roles and localisations of meiotic cohesin subunits may reflect this aspect of cohesin function. Indeed, only some of the flavours of cohesin expressed in oocytes function in sister chromatid cohesion during the meiotic divisions. Sister chromatid cohesion in metaphase I mouse oocytes depends on an intact REC8 kleisin subunit suggesting that any cohesin complexes that contain the meiotic RAD21L or mitotic RAD21 kleisins are not sufficient to generate functional sister chromatid cohesion in these cells [56]. In contrast, some functional sister chromatid cohesion can be generated in meiotic oocytes lacking the meiotic SMC1 β cohesin, presumably by cohesin complexes containing the mitotic SMC1 α cohesin [57]. The ability of mitotic cohesins to function in sister chromatid cohesion in meiotic oocytes may be related to differences in the way that different cohesin subunits, and different flavours of cohesin subunit, are regulated.

4.2. Establishment of cohesion

Studies in yeast and mammalian mitotic cells have revealed that cohesin loading onto DNA during DNA replication requires the heterodimeric cohesin loading factor NIPBL-MAU2 [58,59]. Cohesin is

loaded onto DNA through the opening of an entry gate at the interface of the SMC1 and SMC3 subunits. Once loaded, cohesin can be released from DNA by opening an exit gate at the interface of the SMC3 and kleisin subunits [58,59]. Loading cohesin onto chromatin is required but not sufficient for cohesion to be established between sister chromatids. During establishment of cohesion, acetylation of SMC3 by the acetyltransferase ECO1 leads to the recruitment of sororin which promotes sister chromatid cohesion by displacing WAPL from its interacting partner PDS5, and preventing WAPL-dependent removal of cohesin from the chromatin [58–61]. The recruitment of sororin therefore locks the loaded-cohesin complexes onto DNA and marks a sub-population of cohesin that is more tightly associated with chromatin [62]. It is not yet known whether SMC3 acetylation occurs during the establishment of sister chromatid cohesion in mammalian oocytes, or if sororin plays a role in protecting any acetylated SMC3-marked cohesin from WAPL-mediated dissociation. However, any genetic variation or environmental influences during human foetal development that alter the activity of the genes involved in the establishment of meiotic cohesion could potentially affect the incidence of aneuploidy in adult oocytes.

4.3. Cohesin removal

During mammalian mitosis, removal of cohesin occurs in two discrete steps [63]. Firstly, phosphorylation of cohesin and shugoshin by the prophase pathway allows WAPL to remove cohesin from chromosome arms by a non-proteolytic mechanism, whilst centromeric cohesin is protected by a complex of shugoshin and protein phosphatase 2A (SGO1-PP2A) [58,59,61]. In the second step of mitotic cohesin removal, activation of the anaphase promoting complex at the metaphase-anaphase transition stimulates the ubiquitylation and proteasome-dependent degradation of securin, an inhibitor of separase. Separase then removes centromeric cohesion by proteolytically cleaving the kleisin subunit, triggering anaphase and chromosome segregation [58,59].

In contrast to mitotic cells, removal of arm cohesin in meiosis requires separase-mediated proteolysis of REC8 [64]. It is unknown whether WAPL-mediated cohesin removal occurs in oocytes, however conditional knockdown of separase post-natally in growing oocytes prevents chiasmata resolution and polar body extrusion [64]. Therefore, whether a WAPL pathway operates or not, it is unable to compensate for separase-mediated cohesin removal at anaphase I. As in mitotic cells, shugoshin acts with PP2A in MI to protect centromeric cohesin from separase cleavage [65]. In yeast, SGO-PP2A appears to protect centromeric cohesion during MI by antagonising REC8 phosphorylation which is essential for its cleavage by separase [66], but whether this mechanism is conserved in mammalian oocytes is unknown [66]. Over-expression of SGO1 in mouse oocytes has been shown to block homologous chromosome segregation but only when it is capable of interacting with PP2A [67], thus demonstrating the essential interaction between these proteins. Protection of centromeric cohesion in mouse oocytes is normally mediated by SGO2 shugoshin [65]. Mammalian SGO2 colocalises with centromeric REC8 at metaphase I, where it is stabilised by meikin, a meiosis-specific kinetochore protein that helps protect centromeric cohesion and prevents sister chromatids bi-orienting to opposite spindle poles at this stage [65,68]. SGO2 is redistributed at metaphase II by spindle-associated tension acting across the sister centromeres. This relocation of SGO2/PP2A is thought to permit removal of centromeric REC8 during metaphase II–anaphase II resulting in sister chromatid segregation [65,66]. Clearly, there are fundamental differences in the pathways used to remove arm cohesion in meiosis and mitosis, however some of the proteins involved in protection and cleavage of centromeric cohesin appear to be the same. As will become clear in Section 4.4,

pathways that remove cohesin from meiotic chromosomes in resting dictyate oocytes may play a role in age-dependent aneuploidy in mammalian oocytes.

4.4. Cohesion decay in mice

The cohesion that is established in foetal oocytes needs to be maintained throughout the prolonged dictyate arrest to mediate faithful meiotic chromosome segregation in the adult oocytes. One of the first indications that defects in cohesins play a role in age-related aneuploidy came from studies of mice lacking the meiosis-specific SMC protein, SMC1 β [57,69]. Despite having reduced cohesion at the early stages of chromosome condensation, SMC1 β ^{−/−} oocytes progress through meiosis I to dictyate arrest. Whilst MLH1 foci are normally distributed in SMC1 β ^{−/−} foetal oocytes, there is failure to maintain sister chromatid cohesion as chiasmata position is skewed in adult oocytes, with chiasmata being found in more terminal positions [57]. This reduction in cohesion and terminalisation of chiasmata results in fewer chiasmata, increased frequency of univalent chromosomes, and single chromatids, leading to considerable aneuploidy and consequent sterility [69]. Importantly, comparison of chromosome preparations from one month and two month old mice revealed that the severity of these defects increased with age. Therefore, reduced levels of cohesion in SMC1 β ^{−/−} post-natal oocytes accelerates the appearance of defects similar to those seen in naturally ageing mice.

Interestingly, conditional inactivation of SMC1 β shortly after birth has no effect on sister chromatid cohesion, chiasma placement or fertility in female mice [70]. Similarly, elegant genetic experiments in mice that conditionally express REC8 at different stages of oogenesis demonstrate that REC8 expression post-natally in growing oocytes is not able to function in sister chromatid cohesion during meiosis I [56]. This suggests that cohesion which is lost or removed from oocytes post-natally is not replaced, and that the meiotic cohesins that are loaded onto DNA in foetal life must be maintained in adults.

Different strains of naturally aged mice have a marked reduction in the amount of the meiotic kleisin REC8 on chromosome arms and centromeres in metaphase I oocytes and SMC1 β , is similarly reported to be markedly reduced in older oocytes [45,46,71]. This age related decrease in REC8 and SMC1 β abundance has also been observed in dictyate mouse oocytes suggesting that this deterioration occurs during dictyate arrest [72]. Whether or not the observed changes in REC8 and SMC1 β abundance reflect the behaviour of the entire cohesin complex is unknown, but, consistent with an age-dependent loss of cohesion at centromeres, the distance between sister kinetochores is larger in older oocytes [45,46]. Older oocytes are also less able to maintain chiasmata and have an increased proportion of prometaphase I chromosomes with either a single chiasma located distally on the bivalent, or with no visible chiasmata between univalents that are loosely associated at their telomeres [22,45,46,73]. Migration, terminalisation and loss of chiasmata in older oocytes could potentially reflect weakened sister chromatid cohesion on chromosome arms, particularly cohesion distal to the chiasmata [9]. Therefore, the age-dependent depletion of cohesin from meiotic chromosomes in oocytes appears to be associated with weakening of cohesion along chromosome arms and at centromeres.

The number of single chromatids in old oocytes at metaphase II is much higher than the number of unpaired univalents in prometaphase I suggesting that the primary chromosome segregation error in ageing mouse oocytes involves premature separation of sister chromatids [45,46]. Weakening of centromeric cohesion would allow sister chromatids to either erroneously bi-orient during metaphase I then prematurely separate and segregate at anaphase I (Fig. 2D), or to prematurely separate in anaphase I

after correctly mono-orienting in metaphase I (Fig. 2E). Although a spindle assembly checkpoint operates effectively in young and old oocytes to monitor attachment of chromosomes to the meiosis I spindle, bi-orientation of sister chromatids during meiosis I is not detected by this checkpoint [6,45,46,74]. However, weakening of arm cohesion may play a role in the premature separation of sister chromatids in ageing mouse oocytes as live imaging suggests that bi-orientation and premature separation of sister chromatids on the meiosis I spindle may be preceded by bivalent chromosomes prematurely resolving into transient univalents during metaphase I (Fig. 2C) [47]. The loss of cohesion from meiotic chromosomes in oocytes from older mice could therefore potentially account for at least some of the chromosome missegregation and aneuploidy associated with maternal ageing.

In oocytes, sister chromatids are normally prevented from separating prematurely during metaphase I–anaphase I by SGO2 [65], and loss of chromosome cohesion in aged oocytes correlates with reduced levels of SGO2 on meiotic chromosomes during both MI and MII [46,73]. Interestingly, SGO2 has also been found to localise to chromosome arms, as well as centromeres in metaphase I oocytes, suggesting that SGO2 may also play a role in protecting arm cohesin in meiosis I before the onset of anaphase [46]. The levels of both arm and centromeric associated SGO2 are also reduced in SMC1 β ^{−/−} oocytes, suggesting that cohesin depletion during prolonged dictyate arrest results in reduced recruitment of SGO2, which may in turn amplify loss of cohesion as oocytes age [46].

4.5. Cohesion decay in humans

Similar to the findings from naturally aged mice, immunofluorescent staining of human oocytes in ovarian sections has shown that the level of meiosis-specific cohesins, REC8 and SMC1 β are decreased in dictyate oocytes in small follicles from older women [72]. Whether or not there is a reduction in arm cohesin, centromeric cohesin or both in the human oocytes is unclear. Consistent with a reduction in cohesin however, inter-kinetochore distances increase significantly and chromosome segregation errors occur more frequently in human eggs with advanced age [47,75]. Cohesin levels and loss of cohesion shows a linear negative correlation with oocyte age [72] however, the frequency of chromosome segregation errors rises exponentially in women in their mid-thirties [4]. Consistent with the findings in naturally aged mice [45], it seems that a threshold level of cohesin is also required in human oocytes in order to prevent missegregation [72]. Interestingly, aside from the age-effect, the rate of cohesion decrease varied between individuals which could indicate that genetic or environmental variation between individuals could be influencing susceptibility to age-dependent oocyte aneuploidy [72]. Clearly, studies from both human and mouse oocytes suggest that loss of chromosome-associated cohesins leads to weakening of cohesion and meiotic errors. However, further research is required to establish if cohesins are being removed from chromosomes during oocyte ageing by one of the known pathways for cohesin removal, by non-specific processes, such as oxidative damage or spontaneous hydrolysis of peptides bonds, or by as yet unidentified mechanisms.

5. Conclusions

It is becoming clear that the developmental strategy used by mammalian oocytes plays a significant part in the high rates of age-dependent maternal aneuploidy seen in humans. Events that occur in foetal oocytes such as failure to form a crossover, or crossover formation in a susceptible location, can lead to chromosome segregation errors and aneuploidy in adult oocytes. As maternal

age increases, maintaining chiasmata and sister chromatid cohesion becomes more of an issue and mechanisms that promote loss of these in post-natal oocytes have a stronger influence on the incidence of oocyte aneuploidy. Huge progress has been made in recent years in our molecular understanding of how sister chromatid cohesion is established, generated and removed during meiosis, and in deciphering the chromosome segregation defects that contribute to aneuploidy in ageing oocytes. Understanding the primary mechanisms contributing to loss of sister chromatid cohesion in post-natal oocytes would seem to be the next major question that needs to be answered, and is one that will be key if any therapeutic interventions to slow chromosomal ageing in human oocytes are to be developed in the future.

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